

# Molnupiravir

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Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.<sup>1,2</sup>

On December 23, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for molnupiravir for the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral therapies are not accessible or clinically appropriate.<sup>3,4</sup>

Molnupiravir has potent antiviral activity against SARS-CoV-2.<sup>1,5</sup> As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results; in the other study, there was no evidence for mutagenicity.<sup>4</sup> The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.<sup>4</sup> In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA is requiring the manufacturer to establish a process to monitor genomic databases for the emergence of SARS-CoV-2 variants.

## Recommendations

- In nonhospitalized patients aged  $\geq 18$  years who have mild to moderate COVID-19 and who are at high risk of disease progression, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using **molnupiravir** 800 mg orally (PO) twice daily for 5 days **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, or remdesivir cannot be used; treatment should be initiated as soon as possible and within 5 days of symptom onset (**CIIa**).
- The FDA EUA states that molnupiravir is not recommended for use in pregnant patients because fetal toxicity has been reported in animal studies of molnupiravir. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e.,  $>10$  weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy.
- People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. For more details, see the Considerations in Sexually Active Individuals section below.
- There are no data on the use of molnupiravir in patients who have received COVID-19 vaccines. The risk-to-benefit ratio is likely to be less favorable in these patients, because molnupiravir has a lower efficacy compared to other available treatments.

For the Panel's recommendations on using antiviral therapies in outpatients and prioritizing outpatient therapies when there are logistical or supply constraints, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

## Rationale

In the MOVE-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo.<sup>4</sup> Even though the different treatment options have not been directly compared in clinical trials,

the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir, sotrovimab, and remdesivir are not available or cannot be given, because molnupiravir has lower efficacy than the other options. For more information, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

Molnupiravir is expected to be active against the B.1.1.529 (Omicron) variant of concern, although in vitro and in vivo data are currently limited.<sup>6</sup>

### Additional Considerations

- Patients should complete the 5-day treatment course of molnupiravir. It is unknown whether a shorter course is less effective or associated with the emergence of molnupiravir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of molnupiravir can be completed at the health care provider's discretion.
- Molnupiravir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk of progressing to severe disease.
- There are no data on using combination antiviral therapies or combinations of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of SARS-CoV-2 infection.
- Severely immunocompromised patients can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy in treating severely immunocompromised patients is not yet known.

### Considerations in Sexually Active Individuals

Clinicians should assess a patient's pregnancy status before initiating molnupiravir, if clinically indicated.

Patients of childbearing potential should be counseled about abstaining from sex or using reliable contraception for the duration of therapy and for up to 4 days after receiving molnupiravir. Reproductive toxicity has been reported in animal studies of molnupiravir, and molnupiravir may be mutagenic during pregnancy.

The FDA EUA states that men of reproductive potential who are sexually active with individuals of childbearing potential should be counseled to abstain from sex or use a reliable method of contraception for the duration of treatment **and for at least 3 months after the last dose of molnupiravir**.

### Considerations in Pregnancy

The FDA EUA states that molnupiravir is not recommended for use in pregnant patients because fetal toxicity has been reported in animal studies of molnupiravir. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred, and that the patient chose this therapy. The patient should also be informed about the pregnancy surveillance program and offered the opportunity to participate.

There is currently a lack of data on the use of molnupiravir in lactating people, and molnupiravir may

cause adverse effects in infants who are exposed to the drug through breastfeeding. Because of this, the FDA EUA states that lactating people should not breastfeed their infants during treatment with molnupiravir and for 4 days after the final dose. Pumping and discarding breast milk to maintain supply during this time is recommended.

## Considerations in Children

The MOVE-OUT trial excluded participants aged <18 years. There are no data available on the use of molnupiravir in children aged <18 years. Molnupiravir is not authorized for use in children aged <18 years due to potential effects on bone and cartilage growth.

## Monitoring, Adverse Effects, and Drug Interactions

The most common adverse effects of molnupiravir are diarrhea, nausea, and dizziness. Based on in vitro studies, neither molnupiravir nor its active metabolite NHC are inhibitors or inducers of major drug-metabolizing enzymes or inhibitors of major drug transporters. According to the EUA, no drug-drug interactions have been identified for molnupiravir.

## Clinical Trial Data

MOVE-OUT was a multinational, Phase 3 trial that evaluated the use of molnupiravir in nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progressing to severe COVID-19. The participants were not pregnant, had not been vaccinated against COVID-19, and were enrolled within 5 days of symptom onset. They were randomized to receive molnupiravir 800 mg PO every 12 hours for 5 days or placebo.<sup>7</sup> The primary composite outcome was all-cause hospitalizations (defined as hospital stays that lasted >24 hours) and deaths by Day 29.

The final analysis included 1,433 participants; the median age was 43 years (with 17% aged >60 years). Forty-nine percent of the participants were men, 57% were White, 50% were Hispanic/Latinx, and 5% were Black or African American. Among the participants, 74% had a body mass index  $\geq 30$  and 16% had diabetes. The time from COVID-19 symptom onset to randomization was  $\leq 3$  days in 48% of participants.

By Day 29, hospitalizations or deaths had occurred in 48 of 709 participants (6.8%) in the molnupiravir arm and in 68 of 699 participants (9.7%) in the placebo arm (30% relative risk reduction; -3.0% adjusted difference; 95% CI, -5.9% to -0.1%;  $P = 0.0218$ ).<sup>4</sup> There was 1 death in the molnupiravir arm and 9 deaths in the placebo arm. There were no significant differences between the arms in the proportion of participants who experienced adverse events or serious adverse events.

## References

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